PCT/EP2004/014682

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed Steph Hardy

Dated 28 October 2004

PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
A
24 DEC 2003
LONDON

The Patent Office

1/77

28DEC03 E862170-1 000245
P01/7700 0.00-0330031.6 ACCOUNT CHA

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales NP10 8QQ

1. Your reference — **4-33566P1**

24 DEC 2003

2. Patent application number *(The Patent Office will fill in this part)* — 0330031.6

3. Full name, address and postcode of the or of each applicant *(underline all surnames)* — **NOVARTIS AG**
LICHTSTRASSE 35
4056 BASEL
SWITZERLAND

Patent ADP number *(if you know it)* — 7125487005

If the applicant is a corporate body, give the country/state of its incorporation — **SWITZERLAND**

4. Title of invention — **Organic Compounds**

5. Name of your agent *(If you have one)* — **Craig McLean**

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* — **Novartis Pharmaceuticals UK Limited**
Patents and Trademarks
Wimblehurst Road
Horsham, West Sussex
RH12 5AB

Patents ADP number *(if you know it)* — **07181522002**

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day/month/year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

(see note (d))

Yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	17 ✓
Claim(s)	2 ✓
Abstract	1 ✓
Drawing(s)	

CF

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature — Date

Craig McLean — 24th December 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Mr. Trevor Drew — (01403) 323069

Warning

After an application for a patent has been filed. the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the united Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

d) *Once you have filled in the form you must remember to sign and date it.*

e) *For details of the fee and ways to pay please contact the Patent Office.*

DUPLICATE

Organic Compounds

The present invention relates to a device implantable into a human or animal body comprising a biodegradable polymer as well as the use of such device for the controlled release of a pharmacologically active agent for treating or preventing neointimal proliferation and thickening, restenosis and/or vascular occlusion following vascular injury or for promoting tissue healing.

Many humans suffer from circulatory diseases caused by a progressive blockage of the blood vessels that perfuse the heart and other major organs. Severe blockage of blood vessels in such humans often leads to ischemic injury, hypertension, stroke or myocardial infarction. Atherosclerotic lesions which limit or obstruct coronary or periphery blood flow are the major cause of ischemic disease related morbidity and mortality including coronary heart disease and stroke. To stop the disease process and prevent the more advanced disease states in which the cardiac muscle or other organs are compromised, medical revascularization procedures such as percutaneous transluminal coronary angioplasty (PCTA), percutaneous transluminal angioplasty (PTA), atherectomy, bypass grafting or other types of vascular grafting procedures are used.

Re-narrowing (e.g. restenosis) of an artherosclerotic coronary artery after various revascularization procedures occurs in 10-80% of patients undergoing this treatment, depending on the procedure used and the aterial site. Besides opening an artery obstructed by atherosclerosis, revascularization also injures endothelial cells and smooth muscle cells within the vessel wall, thus initiating a thrombotic and inflammatory response. Cell derived growth factors such as platelet derived growth factor, infiltrating macrophages, leukocytes or the smooth muscle cells themselves provoke proliferative and migratory responses in the smooth muscle cells. Simultaneous with local proliferation and migration, inflammatory cells also invade the site of vascular injury and may migrate to the deeper layers of the vessel wall. Proliferation/migration usually begins within one to two days post-injury and, depending on the revascularization procedure used, continues for days and weeks.
Both cells within the atherosclerotic lesion and those within the media migrate, proliferate and/or secrete significant amounts of extracellular matrix proteins. Proliferation, migration and extracellular matrix synthesis continue until the damaged endothelial layer is repaired at which time proliferation slows within the intima. The newly formed tissue is called neointima, intimal thickening or restenotic lesion and usually results in narrowing of the vessel lumen.

Further lumen narrowing may take place due to constructive remodeling, e.g. vascular remodeling, leading to further intimal thickening or hyperplasia.

There are also atherosclerotic lesions which do not limit or obstruct vessel blood flow but which form the so-called "vulnerable plaques". Such atherosclerotic lesions or vulnerable plaques are prone to rupture or ulcerate, which results in thrombosis and thus produces unstable angina pectoris, myocardial infarction or sudden death. Inflamed atherosclerotic plaques can be detected by thermography.

Complications associated with vascular access devices is a major cause of morbidity, for example in hemodialysis patients, e.g. caused by outflow stenoses in the venous circulation. Venous neointimal hyperplasia characterized by stenosis and subsequent thrombosis accounts for the overwhelming majority of pathology resulting in dialysis graft failure. Vascular access related morbidity was found to account for about 23 percent of all hospital stays for advanced renal disease patients and to contribute to as much as half of all hospitalization costs for such patients. Additionally, vascular access dysfunction in chemotherapy patients is generally caused by outflow stenoses in the venous circulation and results in a decreased ability to administer medications to cancer patients. Often the outflow stenoses is so severe as to require intervention. Additionally, vascular access dysfunction in total parenteral nutrition (TPN) patients is generally caused by outflow stenoses in the venous circulation and results in reduced ability to care for these patients.

Up to the present time, there has not been any effective treatment for the prevention or reduction of vascular access dysfunction that accompany the insertion or repair of an indwelling shunt, fistula or catheter, such as a large bore catheter, into a vein in a mammal, particularly a human patient.

Stents have been found to be useful instead of or along with angioplasty to reduce the renarrowing of an artery that occurs after balloon angioplasty or other procedures that use catheters. Stents help restore normal blood flow and keep an artery open after the intervention with the balloon catheter, however, restenosis (reclosure) is also a problem with the stent procedure. Reocclusion following stenting may be due to both restenotic lesion formation within the stent boundaries and constrictive remodeling at both the proximal and distal margins of the local delivery device or system, e.g. stent.

Recently stents have been proposed which are coated with drugs that are slowly released and help keep the vessel from reclosing. However, major obstacles associated with drug-coated stents are the biodegradability of the polymer in which the drug may be incorporated and the biocompatibility of the surfaces of the medical devices. Further important for the long-term success of the procedure are the mechanical properties of the polymer.

Accordingly, there continues to exist a need for effective treatment and drug delivery systems for revascularization procedure, e.g. for preventing or treating intimal thickening or restenosis that occurs after injury, e.g. vascular injury, including e.g. surgical injury, e.g. revascularization-induced injury, e.g. also in heart or other grafts, for a stabilization procedure of vulnerable plaques, or for the prevention or treatment of vascular access dysfunctions.

In accordance with the present invention it has now surprisingly been found that a superior medical device implantable into a human or animal body may be obtained by coating with a biodegradable polymer which comprises ethylene carbonate units of the formula -(-C(O)-O-CH_2-CH_2-O-)- having an ethylene carbonate content of 70 to 100 Mol%, an intrinsic viscosity of 0.4 to 4.0 dl/g measured in chloroform at 20°C at a concentration of 1 g/dl and a glass transition temperature of from 15 to 50°C, degradeable in water by surface erosion which is governed by a non-hydrolytic mechanism. It has been found that the polymer used to coat the device of the invention shows superior biocompatibility, biodegradability, and mechanical properties, e.g. viscoelasticity, as well as superior release characteristics of a pharmacologically active agent incorporated, e.g. dissolved or dispersed, in the polymer. According to the invention it has been found that this unique combination of properties can be exploited to improve the long-term success of procedures, e.g. stenting or other grafting procedures, as hereinabove decribed.

By "biocompatible" is meant a material which elicits no or minimal negative tissue reaction including e.g. thrombus formation and/or inflammation.

In accordance with the particular finding of the present invention, there is provided a device comprising a biodegradable polymer which comprises ethylene carbonate units of the formula A

-(-C(O)-O-CH_2-CH_2-O-)- A

having an ethylene carbonate content of 70 to 100 Mol%, an intrinsic viscosity of 0.4 to 4.0 dl/g measured in chloroform at 20°C at a concentration of 1 g/dl and a glass transition temperature of from 15 to 50°C, degradeable in water by surface erosion which is governed by a non-hydrolytic mechanism, hereinafter referred to as device of the invention.

The medical device may be chosen from catheters, guide wires, balloons, filters, vascular grafts, graft connectors, tubing, implants, sutures, surgical staples, stentgrafts and stents. Preferably, the medical device is a stent.

The stent according to the invention can be any stent, including self-expanding stent, or a stent that is radially expandable by inflating a balloon or expanded by an expansion member, or a stent that is expanded by the use of radio frequency which provides heat to cause the stent to change its size.

Stents may be commonly used as a tubular structure left inside the lumen of a duct or vessel to relieve an obstruction. They may be inserted into the duct lumen in a non-expanded form and are then expanded autonomously (self-expanding stents) or with the aid of a second device in situ, e.g. a catheter-mounted angioplasty balloon which is inflated within the stenosed vessel or body passageway in order to disrupt the obstructions associated with the wall components of the vessel and to obtain an enlarged lumen. Alternatively, stents being easily deformed at lower temperature to be inserted in the hollow tubes may be used: after deployment at site, such stents recover their original shape and exert a retentive and gentle force on the internal wall of the hollow tubes, e.g. of the esophagus or trachea.

Any commercially available stent may be used, e.g. JOSTENT® Flex, JOMED, JOSTENT® SelfX, JOSTENT® Peripheral, JOSTENT® Renal, Biodivysion™ (Biocompatibles Ltd., UK), BX high velocity Stainless Steel L316™ (Cordis, Johnson & Johnson Co., USA), NIR Primo Stainless Steel 316L™, NIRoyal Stainless Steel 316L™ (coated with a 7 μm layer of gold-plating), Radius self-expanding Nitinol™ stent (Medinol, Scimed, Boston Scientific Co., USA), S6™ and S7™ (AVE, Metronic, USA), Multilink Duett™ and Ultra™ (ACS, Guidant S.A., Belgium).

The exterior surface of the device may consist of metal, e.g. gold, silver, platinum, stainless steel, nickel, titanium and biocompatible alloys thereof, or a biodegradable or biocompatible organic or inorganic polymer, e.g. fibrin, polytetrafluoroethylene (PTFE), silicone, silicone rubber, nylon and polyethylene perthalate (Dacron).

The polymer used in the device of the invention and its process of manufacture are disclosed in WO 95/06077, the subject matter of which, in particular with respect to the polymer and its process of manufacture, are hereby incorporated into the present application by reference to this publication.

The ethylene carbonate content of the polymer used according to the invention is from 70 to 100 Mol%, particularly 80-100%, preferably from 90-99.9%, such as from 94 to 99.9%. The intrinsic viscosity of the (co)-polymer is from 0.4 to 4.0 dl/g, measured in chloroform at 20°C and a concentration of 1 g/dl in chloroform of 0.4 to 3.0 dl/g. Its glass transition temperature is from 15° to 50°C, preferably from 18° to 50°C.
As a consequence of their production method the (co)-polymers contain in most cases as a co-unit the ethylene oxide unit of the formula B

$$-(-CH_2-CH_2-O-)- \qquad B$$

In the (co)-polymers used in the invention, if exposed to an aqueous medium, e.g. a phosphate-buffered saline of pH 7.4 practically no medium will be transported to their bulk part. Therefore no bulk erosion will occur and the remaining mass will be kept constant (100%) for a period of at least 28 days. As a consequence of the absence of bulk erosion the loaded polymer is during storage, i.e. before its administration, inaccessible to moisture and remains in the same dry condition in which it has been produced. Its embedded drug, if sensitive to moisture, remains stable.

The (co)-polymer used in the invention is produced by copolymerization of ethylene oxide and CO_2 in a molar ratio of from 1:4 to 1:5 under the influence of a catalyst. In the scope of this reaction the introduction of ethylene oxide units in the (co)-polymer chain is possible, if two epoxide molecules react with each other without intervention of a CO_2 molecule, i.e. if an oxy anion intermediate attacks another ethylene oxide molecule before being carboxylated by CO_2. It is thus probable that the (co)-polymer contains several ethylene oxide units.
The (co)-polymer used in the invention, if containing ethylene oxide units, has a random distribution of ethylene carbonate and ethylene oxide units according to the sum formula
A_m-B_n = $-(C(O)-O-CH_2-CH_2-O-)_m-(-CH_2-CH_2-O-)_n$
in which

$$\frac{m}{n+m} \times 100 = 70 \text{ to } 100.$$

In the process the ethylene oxide unit content and thus the content of ether functions, which delays or inhibits the biodegradation speed of the (co)-polymer, is reduced considerably by specifying the reaction conditions such as the described molar ratio's of the reaction components, the reaction temperature and further by choosing an appropriate catalyst, e.g. such prepared from Zn $(C_2H_5)_2$ and water or acetone or a di- or a triphenol, e.g. phloroglucin, in a molar ratio of from 0.9:1 to 1:0.9 or 2:1 to 1:2 respectively, or preferably prepared from Zn $(C_2H_5)_2$ and a diol, especially ethylene glycol, in a molar ratio of from 0.9:1 to 1:0.9.
The process is preferably carried out in a solvent or dispersing agent system of an organic solvent, e.g. dioxane and CO_2. CO_2 is preferably applied in liquid form and is present in an excess. The pressure is preferably from 20 to 70 bar and the temperature preferably from 10 to 80°C, especially from 20 to 70°C.
The polymers thus obtained comprise usually less than 15% of ether functions, preferably less than 10%, particularly less than 5%, e.g. less than 3%. The poly(ethylenecarbonate)s, if prepared using the catalyst from ethylene glycol or acetone and diethylzinc exhibit low polydispersities (Mw/Mn), usually less than 5, such as less than 2.5.
According to the above process the catalyst or a part of it is considered to be the chain initiator for the (co)-polymer. When the reaction is finished and the chain is complete, its final terminal group is a hydroxyl group. The opposite site of the chain, there where the chain was started up, may be occupied by the catalyst group or a fragment of it. If the catalyst is prepared from ethylene glycol and diethylzinc or water and diethylzinc, both ends of a polymer chain are supposed to be identical. However, if the catalyst is prepared from a di-or triphenol and diethylzinc, the aromatic group will be incorporated into the end of a chain, where the chain starts up, whereas the other end of the chain will be a hydroxyl group. It was shown that poly(ethylene carbonate), if one of its terminal groups is blocked, e.g. by an aromatic initiator such as phloroglucin, is slower biodegradable. For that reason, it is assumed, that the (co)-polymer chain degradation starts at the terminal hydroxyl group(s). Alternatively, a later derivatization of a terminal hydroxyl group may also be considered, e.g. by esterification, to block terminal hydroxyl groups and to control the biodegradation of the poly (ethylene carbonate)s used in the invention. Suitable terminal ester groups are biocompatible ester groups, like $(C_1\text{-}_{48})$ fatty acid ester groups, preferably $(C_1\text{-}_{30})$, especially $(C_1\text{-}_{18})$ fatty acid ester groups, e.g. the ester groups of acetic acid and stearic acid, or a carbonic acid ester group, e.g. the ethylene carbonate group, or the pamoic ester group or a lactic or glycolic or polylactic or polyglycolic or polylactic-co-glycolic acid ester group.

The poly (ethylene carbonate)s used in the invention are stable for several hours in hot water (90-100°C) without considerable molecular weight reduction. A significant increase of the glass transition temperature is observed after exposure to boiling bidistilled water during 5 hours, e.g. up to above 18°C, e.g. 28°C. By performing this reaction step, a higher polymer purity and better processable polymer is attained.

The poly (ethylene carbonate) portion of the (co)-polymers used in the invention is not hydrolysable, i.e. during at least 1 month by hydrolytic enzymes under physiological conditions or by water at pH 12 and 37°C.

However, it was discovered that the (co)-polymers used in the invention degrade in vivo and in vitro by surface erosion under the influence of the superoxide radical anion $O_2^{\cdot -}$.

Superoxide radical anions $O_2^{\cdot -}$ are generated in inflammatory cells in vivo and ex vivo in the presence of the poly (ethylene carbonate)s used in the invention.

The degradation rate of the (co)-polymers of the invention may be adjusted within wide limits, depending on their molecular weight, their ethylene oxide content, the identity of the terminal groups, e.g. biocompatible ester groups, and the presence of $O_2^{\cdot -}$radical scavengers, e.g. vitamin C, and may last between 5 days and 6 months or longer, e.g. up to 1 year. A radical scavenger may be embedded in the (co)-polymer as an additive.

It has been found that those radicals may be present during the restenosis process. Therefore the rate of drug release from the polymer may increase in case of restenosis processes and may slow down in case of reduced restenosis rates.

The molecular weight (Mw) of the (co)-polymers of the invention is from 80,000, preferably from 100,000, particularly from 200,000 to 2,000,000 Daltons, determined by gel permeation chromatography with methylene chloride as the eluant and polystyrene as the reference.

The (co)-polymer used in the device of the invention may be used alone or in combination with another polymer suitable to coat a medical device, e.g. a stent, implantable into a human or animal body. Suitable polymers for use in combination with the polymer used in the device of the invention may be one or more of the following: hydrophilic, hydrophobic or biocompatible biodegradable materials, e.g. polycarboxylic acids; cellulosic polymers; starch; collagen; hyaluronic acid; gelatin; lactone-based polyesters or copolyesters, e.g. polylactide; polyglycolide; polylactide-glycolide; polycaprolactone; polycaprolactone-glycolide; poly(hydroxybutyrate); poly(hydroxyvalerate); polyhydroxy(butyrate-co-valerate); polyglycolide-co-trimethylene carbonate; poly(diaxanone); polyorthoesters; polyanhydrides;

polyaminoacids; polysaccharides; polyphospoeters; polyphosphoester-urethane; polycyanoacrylates; polyphosphazenes; poly(ether-ester) copolymers, e.g. PEO-PLLA, fibrin; fibrinogen; or mixtures thereof; and biocompatible non-degrading materials, e.g. polyurethane; polyolefins; polyesters; polyamides; polycaprolactame; polyimide; polyvinyl chloride; polyvinyl methyl ether; polyvinyl alcohol or vinyl alcohol/olefin copolymers, e.g. vinyl alcohol/ethylene copolymers; polyacrylonitrile; polystyrene copolymers of vinyl monomers with olefins, e.g. styrene acrylonitrile copolymers, ethylene methyl methacrylate copolymers; polydimethylsiloxane; poly(ethylene-vinylacetate); acrylate based polymers or coplymers, e.g. polybutylmethacrylate, poly(hydroxyethyl methylmethacrylate); polyvinyl pyrrolidinone; fluorinated polymers such as polytetrafluoethylene; cellulose esters e.g. cellulose acetate, cellulose nitrate or cellulose propionate.

The (co)-polymers used in the invention are advantageously combined with pharmacologically active agents. For example, the pharmacologically active agents may be incorporated into the polymeric matrix. Since under in vitro and in vivo conditions no bulk erosion occurs and the active compound is protected by the polymer, the active compound is released as soon as it appears at the matrix surface due to surface erosion of the matrix. Advantageously, the size of the pharmacologically active compound molecule does not influence its release rate. However, according to the invention it has been found that different particle sizes may for example be used to influence the release rate. For example, it has been found that the particle size may correlate with the release rate.

In a series of further specific or alternative embodiments the invention also provides a device as hereinabove described further comprising a pharmacologically active agent incorporated, e.g. dissolved or dispersed, in the polymer.

In one aspect the invention provides the controlled, e.g. sustained, delivery of the pharmacologically active agent or sufficient pharmacological activity at or near the coated surfaces of the device.

In yet a further aspect the present invention provides a device as hereinabove described in form of a drug-eluting stent.

The term "sustained release" or "controlled release" as used herein, means that the (co)-polymer used releases no more than 10, 20, 30, 40 or 50% to 60, 70, 80, or 90% by weight

of the pharmacologically active agent dissolved or dispersed therein within 7 days after implantation of the device into a human or animal body.

As used herein, the term "pharmacologically active agent" comprises any substances which may yield a physiological response when administered to a living organism.
According to the invention, the pharmacologically active agent may be chosen from at least one of:

a) an immunosuppressive agent, e.g. a calcineurin inhibitor, e.g. a cyclosporin, for example cyclosporin A, ISA tx 247 or FK506,

b) an EDG-receptor agonist having lymphocyte depleting properties, e.g. FTY720 (2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol in free form or in a pharmaceutically acceptable salt form, e.g. the hydrochloride) or an analogue such as described in WO96/06068 or WO 98/45249, e.g. 2-amino-2-{2-[4-(1-oxo-5-phenylpentyl)phenyl]ethyl}propane-1,3-diol or 2-amino-4-(4-heptyloxyphenyl)-2-methyl-butanol in free form or in a pharmaceutically acceptable salt form,

c) an anti-inflammatory agent, e.g. a steroid, e.g. a corticosteroid, e.g. dexamethasone or prednisone, a NSAID, e.g. a cyclooxygenase inhibitor, e.g. a cox-2 inhibitor, e.g. celecoxib, rofecoxib, etoricoxib or valdecoxib, an ascomycin, e.g. ASM981 (or pimecrolimus), a cytokine inhibitor, e.g. a lymphokine inhibitor, e.g. an IL-1, -2 or –6 inhibitor, for example pralnacasan or anakinra, or a TNF inhibitor, for instance Etanercept, or a chemokine inhibitor;

d) an anti- thrombotic or anti-coagulant agent, e.g. heparin or a glycoprotein IIb/IIIa inhibitor, e.g. abciximab, eptifibatide or tirofibran;

e) an antiproliferative agent, e.g.
a microtubule stabilizing or destabilizing agent including but not limited to taxanes, e.g. taxol, paclitaxel or docetaxel, vinca alkaloids, e.g. vinblastine, especially vinblastine sulfate, vincristine especially vincristine sulfate, and vinorelbine, discodermolides or epothilones or a derivative thereof, e.g. epothilone B or a derivative thereof;
a protein tyrosine kinase inhibitor, e.g. protein kinase C or PI(3) kinase inhibitor, for example staurosporin and related small molecules, e.g. UCN-01, BAY 43-9006, Bryostatin 1, Perifosine, Limofosine, midostaurin, CGP52421, RO318220, RO320432, GO 6976, Isis 3521, LY333531, LY379196, SU5416, SU6668, AG1296, etc. Midostaurin is a derivative of the naturally occurring alkaloid staurosporine with the chemical name (*N*-[(9*S*,10*R*,11*R*,13*R*)-2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1*H*,9*H*-diindolo[1,2,3-gh:3',2',1'-lm]pyrrolo[3,4-j][1,7]benzodiazonin-11-yl]-*N*-

methylbenzamide), and has been specifically described in the European patent No. 0 296 110 published on December 21, 1988, as well as in US patent No. 5;093,330 published on March 3, 1992, and Japanese Patent No. 2 708 047 all in the name of the applicant. Midostaurin was originally identified as an inhibitor of protein kinase C (PKC) (Meyer T, Regenass U, Fabbro D, et al: Int J Cancer 43: 851-856, 1989).

a compound or antibody which inhibits the PDGF receptor tyrosine kinase or a compound which binds to PDGF or reduces expression of the PDGF receptor e.g. a N-phenyl-2-pyrimidine-amine derivative, CT52923, RP-1776, GFB-111, a pyrrolo[3,4-c]-beta-carboline-dione, etc.;

a compound or antibody which inhibits the EGF receptor tyrosine kinase or a compound which binds to EGF or reduces expression of the EGF receptor e.g. EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 97/02266, e.g. the compound of ex. 39, or in EP 0 564 409, WO 99/03854, EP 0520722, EP 0 566 226, EP 0 787 722, EP 0 837 063, US 5,747,498, WO 98/10767, WO 97/30034, WO 97/49688, WO 97/38983 and, especially, WO 96/30347 (e.g. compound known as CP 358774), WO 96/33980 (e.g. compound ZD 1839, Iressa) and WO 95/03283 (e.g. compound ZM105180); e.g. trastuzumab (Herpetin^{R}), cetuximab, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3, retinoic acid, alpha-, gamma- or delta-tocopherol or alpha-, gamma- or delta-tocotrienol, or compounds affecting GRB2, IMC-C225; or

a compound or antibody which inhibits the VEGF receptor tyrosine kinase or a VEGF receptor or a compound which binds to VEGF, e.g. proteins, small molecules or monoclonal antibodies generically and specifically disclosed in WO 98/35958, e.g. 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, e.g. the succinate, or in WO 00/09495, WO 00/27820, WO 00/59509, WO 98/11223, WO 00/27819, WO 00/37502, WO 94/10202 and EP 0 769 947, those as described by M. Prewett et al in Cancer Research 59 (1999) 5209-5218, by F. Yuan et al in Proc. Natl. Acad. Sci. USA, vol. 93, pp. 14765-14770, Dec. 1996, by Z. Zhu et al in Cancer Res. 58, 1998, 3209-3214, by J. Mordenti et al in Toxicologic Pathology, Vol. 27, no. 1, pp 14-21, 1999, Angiostatin™, described by M. S. O'Reilly et al, Cell 79, 1994, 315-328, Endostatin™, described by M. S. O'Reilly et al, Cell 88, 1997, 277-285, anthranilic acid amides, ZD4190; ZD6474, SU5416, SU6668 or anti-VEGF antibodies or anti-VEGF receptor antibodies, e.g. RhuMab;

f) a statin, e.g. having HMG-CoA reductase inhibition activity, e.g. fluvastatin, lovastatin, simvastatin, pravastatin, atorvastatin, cerivastatin, pitavastatin, rosuvastatin or nivastatin;

g) a compound, protein, growth factor or compound stimulating growth factor production that will enhance endothelial regrowth of the luminal endothelium, e.g. FGF, IGF;

h) a matrix metalloproteinase inhibitor, e.g. batimistat, marimistat, trocade, CGS 27023, RS 130830 or AG3340;

k) a modulator (i.e. antagonists or agonists) of kinases, e.g. JNK, ERK1/2, MAPK or STAT;

l) a compound stimulating the release of (NO) or a NO donor, e.g. diazeniumdiolates, S-nitrosothiols, mesoionic oxatriazoles, isosorbide or a combination thereof, e.g. mononitrate and/or dinitrate;

m) a somatostatin analogue, e.g. octreotide, lanreotide, vapreotide or a cyclohexapeptide having somatostatin agonist properties, e.g. cyclo[4-(NH_2-C_2H_4-NH-CO-O)Pro-Phg-DTrp-Lys-Tyr(Bzl)-Phe]; or a modified GH analogue chemically linked to PEG, e.g. Pegvisomant;

n) an altosterone synthetase inhibitor or aldosterone receptor blocker, e.g. eplerenone, or a compound inhibiting the renin-angiotensin system, e.g. a renin inhibitor, e.g. SPP100, an ACE inhibitor, e.g. captopril, enalapril, lisinopril, fosinopril, benazepril, quinapril, ramipril, imidapril, perindopril erbumine, trandolapril or moexipril, or an ACE receptor blocker, e.g. losartan, irbesartan, candesartan cilexetil, valsartan or olmesartan medoxomil;

o) mycophenolic acid or a salt thereof, e.g. sodium mycophenolate, or a prodrug thereof, e.g. mycophenolate mofetil.

p) a rapamycin derivative. Rapamycin is a known macrolide antibiotic produced by Streptomyces hygroscopicus, which inhibits mTOR. By rapamycin derivative having mTOR inhibiting properties is meant a substituted rapamycin, e.g. a 40-substituted-rapamycin or a 16-substituted rapamycin, or a 32-hydrogenated rapamycin. Representative rapamycin derivatives are e.g. 32-deoxorapamycin, 16-pent-2-ynyloxy-32-deoxorapamycin, 16-pent-2-ynyloxy-32(S or R)-dihydro-rapamycin, 16-pent-2-ynyloxy-32(S or R)-dihydro-40-O-(2-hydroxyethyl)-rapamycin, 40-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]-rapamycin (also called CCI779) or 40-epi-(tetrazolyl)-rapamycin (also called ABT578). A preferred compound is e.g. 40-0-(2-hydroxyethyl)-rapamycin disclosed in Example 8 in WO 94/09010, or 32-deoxorapamycin or 16-pent-2-ynyloxy-32(S)-dihydro-rapamycin as disclosed in WO 96/41807. Rapamycin derivatives may also include the so-called rapalogs, e.g. as disclosed in WO 98/02441 and WO01/14387, e.g. AP23573.

The above list further comprises the pharmaceutically acceptable salts, the corresponding racemates, diastereoisomers, enantiomers, tautomers as well as the corresponding crystal

modifications of above disclosed compounds where present, e.g. solvates, hydrates and polymorphs. Further comprised are metabolites and drug-conjugates.
By antibody is meant monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.

The preferred pharmacologically active agents according to the invention are chosen from at least one of a rapamycin derivative having mTOR inhibiting properties or rapamycin, an EDG-receptor agonist having lymphocyte depleting properties, a cox-2 inhibitor, pimecrolimus, a cytokine inhibitor, a chemokine inhibitor, an antiproliferative agent, a statin, a protein, growth factor or compound stimulating growth factor production that will enhance endothelial regrowth of the luminal endothelium, a matrix metalloproteinase inhibitor, a somatostatin analogue, an aldosterone synthetase inhibitor or aldosterone receptor blocker and a compound inhibiting the renin-angiotensin system. Most preferably pharmacologically active agents selected from a calcineurin inhibitor, mycophenolic acid, rapamycin and midostaurin or a salt thereof or prodrug thereof, may be used.

According to the invention any of the above listed compounds, alone or in combination, or any other compound useful in the treatment or prevention of neointimal proliferation and thickening, restenosis and/or vascular occlusion following vascular injury, vascular access dysfunction or for promoting tissue healing may be used for incorporation into the polymer used in the device of the invention.

In a further aspect the invention provides a device coated with a (co)-polymer as defined herein comprising a pharmacologically active agent as described above, showing non-hydrolytic surface erosion, especially with a linear, especially a 1:1 linear correlation of active compound release and non-hydrolytic (co)-polymer mass degradation and active compound protection in the (co)-polymer matrix.

In a further aspect of the invention, the composition comprising the (co)-polymer and the pharmacologically active agent may further comprise pharmaceutically acceptable adjuvants, e.g. ionic or non-ionic surfactants, adhesives, stabilizers, antioxidants, lubricants and/or pH regulators. It will be appreciated that such further ingredients are well known in the art.

The pharmacologically active agent may be present in a concentration of from 0.01 to 99 % by weight (wt%). The typical dosage of the pharmacologically active agent varies within a wide range and depends on various factors, such as the particular requirements of each receiving individual, the used active agent, the circumstance under which it is applied, and the particular medical device used. The dosage is generally within the range of 0.001-100 mg/kg body weights, however, certain circumstances may require other ranges.

The local delivery according to the present invention allows for high concentration of the drug(s) at the disease site with low concentration of circulating compound. The amount of drug(s) used for local delivery applications will vary depending on the compounds used, the condition to be treated and the desired effect. For purposes of the invention, a therapeutically effective amount will be administered; for example, the drug delivery device or system is configured to release the active agent and/or the active co-agent at a rate of 0.001 to 800 µg/day, preferably 0.001 to 200 µg/day. By therapeutically effective amount is intended an amount sufficient to inhibit cellular proliferation and resulting in the prevention and treatment of the disease state. Specifically, for the prevention or treatment of vascular problems e.g. after revascularization, or antitumor treatment, local delivery may require less compound than systemic administration.

A contemplated treatment period for use in the present invention may be from about 14 to about 85 days, e.g. about 28, 50 or 70 days, in association with the insertion or repair of a stent, an indwelling shunt, fistula or catheter.

The polymer layer coated onto the device may have a thickness in the range of from about 0.1 to 1000 μm, e.g. at least about 0.5 μm, e.g. from about 1 to 20µm.
In one aspect of the invention, the thickness of the polymer layer may, advantageously, may be used to influence the release rate of the pharmacologically active agent. For example, it has been found that the thickness of the layer may be inversely related to the release rate.

In a further or alternative embodiment the invention also provides a use of a device as described herein for treating or preventing neointimal proliferation and thickening, restenosis and/or vascular occlusion following vascular injury or for promoting tissue healing.

In yet a further aspect there is also provided a method for treating or preventing neointimal proliferation and thickening, restenosis and/or vascular occlusion following vascular injury or for promoting tissue healing in a human or animal body comprising implanting of a device as described herein into a site where such treatment, prophylaxis or tissue healing is required.

In accordance with the particular findings of the present invention, there is further provided a method for preventing, treating, reducing or stabilizing
(i) smooth muscle cell proliferation and migration in hollow tubes, e.g. catheter-based device, or increased cell proliferation or decreased apoptosis or increased matrix deposition;
(ii) intimal thickening in vessel walls, e.g. remodeling, hypertrophic remodeling, matrix deposition, fibrin deposit, neointima growth, stenosis, restenosis, e.g. following revascularization or neovascularization, and/or inflammation and/or thrombosis;
(iii) inflammatory disorders, e.g. T-cell induced inflammation, in hollow tubes;
(iv) stabilizing vulnerable plaques in blood vessels;
(v) restenosis, e.g. in diabetic or hypertensive patients;
(vi) vascular access dysfunction, e.g. in dialysis, e.g. hemodialysis, patients,
(vii) arterial or venous aneurisms;
(viii) anastomic hyperplasia;
(ix) arterial, e.g. aortic, by-pass anastomosis;
in a subject in need thereof which method comprises the use, e.g. insertion or repair, of a device, e.g. any catheter-based device, e.g. indwelling shunt, fistula or catheter, e.g. a large bore catheter, intraluminal medical device, or adventitial medical device, e.g. into a vein or artery, wherein the device is coated with the polymer as hereinabove described, e.g. in conjunction with one or more pharmacologically active ingredients, e.g. as hereinabove described.

In a further aspect the invention provides a drug delivery device or system comprising (a) a medical device adapted for local application or administration in hollow tubes, e.g. a catheter-based delivery device, e.g. an indwelling shunt, fistula or catheter, or a medical device intraluminal or outside of hollow tubes such as an implant or a sheath placed within the adventitia, coated with the polymer as described herein and (b) a therapeutic dosage of a pharmacologically active agent incorporated into the polymer.

Such a local delivery device or system can be used to reduce the herein mentioned vascular injuries e.g. stenosis, restenosis, or in-stent restenosis, as an adjunct to revascularization,

bypass or grafting procedures performed in any vascular location including coronary arteries, carotid arteries, renal arteries, peripheral arteries, cerebral arteries or any other arterial or venous location, to reduce anastomic stenosis or hyperplasia, including in the case of arterial-venous dialysis access, or in conjunction with any other heart or transplantation procedures, or congenital vascular interventions.

In yet a further aspect the invention provides a device coated with a polymer as defined hereinabove for use in any method as defined under (i) to (ix).

The invention further provides the use of a a biodegradable polymer, comprising ethylene carbonate units of the formula -(-C(O)-O-CH_2-CH_2-O-)- having an ethylene carbonate content of 70 to 100 Mol%, an intrinsic viscosity of 0.4 to 4.0 dl/g measured in chloroform at 20°C at a concentration of 1 g/dl and a glass transition temperature of from 15 to 50°C, degradeable in water by surface erosion which is governed by a non-hydrolytic mechanism, optionally in conjunction with a pharmacologically active agent, for the coating of a device, e.g. a medical device, e.g. a stent, e.g. for use in any method as defined under (i) to (ix).

In a further aspect there is provided a process for the production of a device of the invention comprising coating the device with the ethylene carbonate polymer defined herein.

For example, the pharmacologically active agent(s) may be incorporated into e.g. a polymer or a polymeric matrix and sprayed onto the outer surface of the stent. A mixture of the drug(s) and the polymeric material may be prepared in a solvent or a mixture of solvents and applied to the surfaces of the stents also by dip-coating, brush coating and/or dip/spin coating, the solvent (s) being allowed to evaporate to leave a film with entrapped drug(s).

Utility of the device of the invention in treating, preventing, promoting or stabilizing conditions as hereinabove described, may be demonstrated in animal tests or standard clinical trials, for example using dosages of pharmacologically active agents within the range of 0.001 – 100 mg/kg body weights. The effect of the device of the invention in treating or preventing neointimal proliferation and thickening, restenosis and/or vascular occlusion following vascular injury or for promoting tissue healing can be monitored by any of the methods known to one skilled in the art, e.g. reduction in the extent of restenotic lesion formation compared with placebo treatment, for example reduction in average neointimal thickness,

neointimal area reduction, and percent arterial stenosis reduction, (neo)intimal and endothelial healing, suppression of in-stent neointimal growth and remodeling, e.g. hypertrophic remodeling, reduction in fibrin deposit.

One animal test may be affected as follows:
A combined angioplasty and stenting procedure is performed in New Zealand White rabbit iliac arteries. Iliac artery balloon injury is performed by inflating a 3.0 x 9.0 mm angioplasty balloon in the mid-portion of the artery followed by "pull-back" of the catheter for 1 balloon length. Balloon injury is repeated 2 times, and a 3.0 x 12 mm stent coated according to the invention is deployed at 6 atm for 30 seconds in the iliac artery. Balloon injury and stent placement is then performed on the contralateral iliac artery in the same manner. A post-stent deployment angiogram is performed. All animals receive oral aspirin 40 mg/day daily as anti-platelet therapy and are fed standard low-cholesterol rabbit chow. Twenty-eight days after stenting, animals are anesthetized and euthanized and the arterial tree is perfused at 100 mmHg with lactated Ringer's for several minutes, then perfused with 10% formalin at 100 mmHg for 15 minutes. The vascular section between the distal aorta and the proximal femoral arteries is excised and cleaned of periadventitial tissue. The stented section of artery is embedded in plastic and sections are taken from the proximal, middle, and distal portions of each stent. All sections are stained with hematoxylin-eosin and Movat pentachrome stains. Computerized planimetry is performed to determine the area of the internal elastic lamina (IEL), external elastic lamina (EEL) and lumen. The neointima and neointimal thickness is measured both at and between the stent struts. The vessel area is measured as the area within the EEL. Data are expressed as mean ± SEM. Statistical analysis of the histologic data is accomplished using analysis of variance (ANOVA) due to the fact that two stented arteries are measured per animal with a mean generated per animal. A $P < 0.05$ is considered statistically significant.

Preferred pharmacologically active agents or combinations of pharmacologically active agents for use in the animal tests or standard clinical trials are those having antiproliferative properties, e.g. taxol, paclitaxel, docetaxel, an epothilone, a tyrosine kinase inhibitor, a VEGF receptor tyrosine kinase inhibitor, a VEGF receptor inhibitor, a compound binding to VEGF, a mTOR inhibitor agent e.g. rapamycin derivatives, e.g. 40-O-(2-hydroxyethyl)-rapamycin, a compound having anti-inflammatory properties, e.g. a steroid, a cyclooxygenase inhibitor.

The polymer used in the device of the invention is biodegradable and shows superior release, tolerability, biocompatibility and mechanical properties. For example, the ethylene carbonate polymer used herein is extremely viscoelastic, for example can be stretched up to 1000% without rupture. The drug release from the device, e.g. stent, can be controlled by the coating composition, e.g. the process for manufacturing the polymer, the amount and/or the particle size of the drug, as well as the amount of superoxid radicals present during a restenosis process. Due to the degradation of the polymer in water by surface erosion which is governed by a non-hydrolytic mechanism, the active compound is protected by the polymer. The active compound will be released during the degradation process and will be completely protected from the blood environment until the polymer erodes. Due to the biocompatibility of the polymer, no or only minor inflammatory reactions occur. Accordingly, the device of the invention shows improved long-term success of the procedure employing the device, e.g. stenting procedure. Preferably the smooth muscle cell proliferation or migration is inhibited or reduced according to the invention immediately proximal or distal to the locally treated or stented area.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following example is, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

Example 1: A stent is manufactured from medical 316LS stainless steel and is composed of a series of cylindrically oriented rings aligned along a common longitudinal axis. Each ring consists of 3 connecting bars and 6 expanding elements. The stent is premounted on a delivery system. The pharmacologically active agent, e.g. 40-O-(2-hydroxyethyl)-rapamycin, e.g. 0.05 to 25 mg/ml, optionally together with 2,6-di-tert.-butyl-4-methylphenol (0.001 mg/ml), is incorporated into a polymer matrix based on a polymer which comprises ethylene carbonate units of the formula -(-C(O)-O-CH_2-CH_2-O-)- having an ethylene carbonate content of 70 to 100 Mol%, an intrinsic viscosity of 0.4 to 4.0 dl/g measured in chloroform at 20°C at a concentration of 1 g/dl and a glass transition temperature of from 15 to 50°C, degradeable in water by surface erosion which is governed by a non-hydrolytic mechanism. The stent is coated with this matrix.

Claims

1. A device comprising a biodegradable polymer which comprises ethylene carbonate units of the formula A

-(-C(O)-O-CH_2-CH_2-O-)- A

having an ethylene carbonate content of 70 to 100 Mol%, an intrinsic viscosity of 0.4 to 4.0 dl/g measured in chloroform at 20°C at a concentration of 1 g/dl and a glass transition temperature of from 15 to 50°C, degradeable in water by surface erosion which is governed by a non-hydrolytic mechanism.

2. The device of claim 1 wherein its surface is coated with the polymer.

3. The device of claim 1 or 2 further comprising a pharmacologically active agent.

4. The device of claim 3 wherein the pharmacologically active agent is dissolved or dispersed in the polymer.

5. The device of claim 3 or 4 containing an immunosuppressant as pharmacologically active agent.

6. The device of any preceding claim in form of a stent.

7. The device of claim 6 in form of a drug-eluting stent.

8. Use of the device of any preceding claim for the controlled release of a pharmacologically active agent.

9. Use of the device of any one of claims 1 to 7 for treating or preventing neointimal proliferation and thickening, restenosis and/or vascular occlusion following vascular injury or for promoting tissue healing.

10. Method for treating or preventing neointimal proliferation and thickening, restenosis and/or vascular occlusion following vascular injury or for promoting tissue healing in a human or animal body comprising implanting of a device of any one of claims 1 to 7 into a site where such treatment, prophylaxis or tissue healing is required.

11. A process for the production of a device of any one of claims 1 to 7 comprising coating the device with the ethylene carbonate polymer.

12. Use of a biodegradable polymer, comprising ethylene carbonate units of the formula A

-(-C(O)-O-CH_2-CH_2-O-)- A

having an ethylene carbonate content of 70 to 100 Mol%, an intrinsic viscosity of 0.4 to 4.0 dl/g measured in chloroform at 20°C at a concentration of 1 g/dl and a glass transition temperature of from 15 to 50°C, degradeable in water by surface erosion which is governed by a non-hydrolytic mechanism for the coating of a device.

Abstract

A device implantable into a human or animal body comprising a biodegradable polymer which comprises ethylene carbonate units of the formula A

-(-C(O)-O-CH_2-CH_2-O-)- A

having an ethylene carbonate content of 70 to 100 Mol%, an intrinsic viscosity of 0.4 to 4.0 dl/g measured in chloroform at 20°C at a concentration of 1 g/dl and a glass transition temperature of from 15 to 50°C, degradeable, in water by surface erosion which is governed by a non-hydrolytic mechanism.